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Osteoporosis in patients with rheumatoid arthritis at Chris Hani Baragwanath Academic Hospital

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RESEARCH PROPOSAL: M.MED INTERNAL MEDICINE

Osteoporosis in patients with Rheumatoid Arthritis at Chris Hani Baragwanath Academic Hospital

Dr. Tania Naidoo

A research report submitted to the University of the Witwatersrand, in fulfilment for the requirements of the degree of Master of Medicine in the branch of Internal Medicine

Johannesburg 2022

DECLARATION

I, Tania Naidoo, declare that this research report is my own work which is being submitted for the degree Master of Medicine (in the submissible format with my protocol and an extended literature review) in the branch of Internal Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University



……

22nd day of November 2022

ACKNOWLEDGMENTS:

Heartfelt thanks go to my supervisors.

Dr. Nimmisha Govind and Dr L Winchow, thank you for agreeing to be my supervisors at a late stage. Your patience and understanding of life through the years has been immeasurable.

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To my son Theshanthan. I hope that one day you will realise the time I took from you to complete this was for you and your future.

To my family, thank you for your understanding and support.

To my late Dad, Mr. A B Naidoo educator, thank you for giving me the tools to accomplish this.

ABSTRACT

Background

Osteoporosis is a common comorbidity associated with rheumatoid arthritis (RA). The aim of this study was to determine the risk factors and possible predictors of osteoporosis in black patients with RA.

Methods

One hundred and twenty RA patients, 60 patients with and 60 without osteoporosis were studied. The demographics, disease activity, American college of Rheumatology (ACR) functional status, treatment and Dual Energy X-Ray Absorptiometry (DEXA)-characteristics were then compared.

Results

The mean age of the overall cohort was 66.6 ± 9.5 years, majority (95.5%) were female, of which 97.4% were postmenopausal. The mean disease duration from diagnosis to the DEXA was 8.6 ± 6.2 years. Rheumatoid Factor (RF) positivity was 89.2% and Anti-cyclic Citrullinated Peptide (ACCP) positivity was 82.7%. The median (IQR) for Disease Activity Score 28 swollen and tender joint count using the erythrocyte sedimentation rate (DAS-28 ESR) was 3.4 (2.8-4.7) and the median (IQR) for ESR was 41(22,64.3) mm/hr ~~mmHg~~. There were significantly more patients treated with triple therapy in the no osteoporosis group 38 (63.3%) than the osteoporosis group 21 (35%) (p = 0.00). The ACR functional class was significantly worse in the RA patients with osteoporosis than the RA without osteoporosis [median (IQR), 2 (2, 3) vs 2 (1, 2), (p = 0.03, respectively.

Conclusion

This study found that worse ACR functional class was significantly associated with osteoporosis. In addition, the use of triple therapy had a protective effect. Early recognition of the risk factors for osteoporosis should be sought, with prompt preventative measures, screening and treatment.

ABBREVIATIONS

AOT	Antiosteoporosis treatment
ACCP	Anti-cyclic Citrullinated Peptide
ACR	American College of Rheumatology
BMD	Bone Mineral Density
BMI	Body Mass Index
BSA	Black South African
CHBAH	Chris Hani Baragwanath Academic Hospital
CHQ	Chloroquine
CRF	Clinical Risk Factor
CRP	C Reactive Protein
DAS	Disease Activity Score
DEXA	Dual Energy X-Ray Absorptiometry
DMARDs	Disease-modifying Anti-rheumatic drugs
ESR	Erythrocyte Sedimentation Rate
FRAX®	Fracture Risk Assessment Tool
HAQ	Health Assessment Questionnaire
MTX	Methotrexate
NOFSA	National Osteoporosis Society of South Africa
OP	Osteoporosis
RANK	receptor activator of nuclear factor-ǩβ
RANKL	RANK ligand
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor
SLE	Systemic Lupus Erythematosus

SA	South Africa
WHO	World Health Organisation

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CHAPTER 1 – PROTOCOL AND EXTENDED LITERATURE REVIEW

1.1 Introduction

Rheumatoid arthritis (RA) is the most common inflammatory arthritis in adults and affects up to 1 percent of the population world-wide [1]. It is a destructive joint disease resulting in substantial pain, significant disability, and impairment of quality of life.

Localised bone loss as evidenced by peri-articular osteopenia and bone erosions, forms part of the radiographic criteria in diagnosing RA in the 1987 American College of Rheumatology (ACR) criteria [2]. However, as in many inflammatory conditions such as systemic lupus erythematosis (SLE), inflammatory bowel disease and chronic obstructive pulmonary disease, generalized osteoporosis and fragility fractures are more common [3]. There is a doubled occurrence of both vertebral and hip fractures in RA patients [4]. Bone erosions in RA predicts future bone destruction leading to generalized bone loss [5].

Osteoporosis (OP) is a recognized co-morbidity of RA and is more frequent than in the general population. The risk of OP is influenced by lifestyle factors such as immobility, malnutrition, low body mass index (BMI), genetic and ethnic factors, and secondary to diseases like RA [5]. Within RA itself, there are several factors that may confer a higher risk, such as ongoing inflammation and the presence of antibodies such as anti-cyclic citrillunated peptide (ACCP).

Table1: Risk Factors for osteoporosis and fractures in RA [5].

General Risk Factors	**RA related risk factors**
Age	Ongoing inflammation
Female gender	Presence of ACCP
Low BMI	Reduced mobility
Family History	Sarcopenia
Fall risk	Glucocorticoid therapy
Smoking and /or Alcohol Use	

1.2 Epidemiology

The general population prevalence of OP ranges from 9% up to 38% in women and from 1% up to 8% in men [6]. In South Africa (SA), according to the National Osteoporosis Foundation of South Arica (NOFSA), the incidence of OP in the white, Asian, and mixed-race population is similar to that of developed countries but more research is required in the SA black population [7]. OP research is lacking in sub-saharan Africa [8]. The burden of many non-communicable diseases especially OP, with a consequent increase in fragility fractures, has increased. This is partly due to increasing urbanization and improved survival rates from Human Immunodeficiency Virus (HIV), resulting in an exponential increase in an older population [9].

A population projection done in 2011 by the International Osteoporosis Foundation [10], showed the proportion of the population of 50 years and over was set to increase from 16% to 28%, and 70 years and over from 3% to 8%. This was thought to be an underestimate as antiretrovirals were extensively rolled out thereafter, increasing survival [10].

The prevalence of OP in RA in Oslo was around 30% (up to 50% in post-menopausal women) [11]. The Italian Study Group found a frequency of OP of 28,8% at the lumbar spine and 36,2% at the femoral neck [12] and The Korean Observational Study Network for Arthritis (KORONA) database, found the frequency of OP in their RA population to be as high as 46,8% [13]. A literature review of RA in India found a prevalence of OP of 22% [14]. Hauser, in 2014, noted that the prevalence of OP in a contemporary cohort of RA patients was 26,5% [15].

Worldwide, OP causes about 9 million fractures a year, equating to 1 fragility fracture every 3 seconds. Fragility fractures are the fourth most debilitating non-communicable disease, outranking ischemic heart disease, dementia, and lung cancer [16]. A fragility

fracture is a dreaded complication of OP. It is a spontaneous fracture sustained after minimal or no identifiable trauma, and often may be the first sign of OP [17].

Previously, it was thought that fracture rates were lower in the black South African (BSA) population, but several recent local studies have shown this to be an incorrect assumption [18,19]. A similar vertebral fracture rate was found in older black and white South African women [18]. Paruk [19] found that the incidence rates of osteoporotic hip fractures were tenfold higher than previously recorded. However, in the latest study on Fracture Risk Assessment Tool (FRAX) based fracture probabilities in South Africa [20], it was found that Black Africans fell in the low-risk category and had slightly lower probability of fracture than Black Americans. The study was limited to a third of the total population (from 8 districts in 3 provinces) and its representation of the entire population could not be tested, and fracture rates may vary in urban versus rural communities.

A meta-analysis consisting of 13 studies on bone fracture risk showed a significantly higher risk in patients with RA compared to patients without RA (RR 2.25, 95% CI (1.76 -2.87)), and this pertained to both male and female patients, as well as to both vertebral and hip fractures [21]. The Total Management of Risk Factors in RA patients to Lower Morbidity and Mortality (TOMORROW) study, found the prevalence of vertebral fractures to be as high as 45,5% in patients with RA [22].

The development of OP in RA patients leads to a further decline in the quality of life and a substantial increase in the costs of rehabilitation and treatment. Fragility fractures yield an enormous economic burden, from the direct burden of hospitalizations and physician visits, which in 2002 ranged from 12.2 to 179 billion US dollars per year, to the indirect costs of reduced productivity due to disability and premature death [23].

In addition, due to high rates of trauma, limited orthopedic facilities and poor socio-economic circumstances, the mortality rate following a hip fracture was as high as 33,5% in a recent local study [24]. After having a fragility fracture, patients usually experience a deterioration in physical and mental health, and many become isolated and depressed with residual chronic pain [23].

1.3 Osteoporosis Definition

OP according World Health Organization (WHO) definition, is a systemic skeletal disease characterized by low bone mass (measured by bone mineral density (BMD)), and micro architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. According to the WHO, it can also be defined as a value of BMD more than -2.5 standard deviations below the young adult normal mean [7].

1.3.1 Osteoporosis Diagnosis

NOFSA (National Osteoporosis Foundation of South Africa) recommends that a diagnosis of OP be made, based on a BMD measurement or the presence of a fragility fracture and should be confirmed before initiating treatment with bone-active drugs. Currently, a dual energy X-ray absorptiometry (DEXA) test is performed at the lumbar spine and the femoral neck, and the lowest BMD value is recorded as either the T-score or the Z-score [7]. The T-score compares individual results to those in a young population that is matched for race and sex. The Z-score compares individual results to those of an age matched population, that is also matched for race and sex. The T-score is expressed as Standard Deviations (SD) below mean for a young control group, and the Z-score as SD below mean for age.

Table 2 : WHO Classification [7].

Definition	Criteria
Normal	BMD or BMC value (measured with DXA at either the spine, total hip or femur neck) within 1 SD of the young adult reference mean (T-score* at or above -1.0)
Low bone mass	BMD or BMC value more than 1 SD, but less than 2.5 (osteopenia) SD below the young adult mean (T-score between -1.0 and - 2.5)
Osteoporosis	BMD or BMC value is 2.5 SD or more below the young adult mean
Severe osteoporosis	BMD or BMC value more than 2.5 SD below the young adult mean, plus one or more fragility fractures

* These criteria were updated in 2008 and differ from those proposed by the WHO in 1994 by specifying a single reference site (the femoral neck) to measure BMD, providing a young normal reference range for women and men (the NHANES III reference data for femoral neck measurements in women aged 20-29 years), and by accommodating diagnostic criteria for men (see 6.2.1 and 6.3).
** When standard deviation (SD) units are used in relation to the young healthy adult population, this is referred to as the T-score.

Mean BMD values in the BSA population is lower than those of African Americans, hence it is suggested that until local reference values are available, Caucasian female data be used as a reference for subjects of all races [7].

A study on the skeletal health among African Americans with recent onset RA, found that 33% of patients had osteopenia and only 4% met criteria for OP as per the National Osteoporosis Foundation. However, although the incidence of OP is lower in African Americans than white Americans, the outcome of any fracture was poorer than the white population due to socio-demographic factors [25]. FRAX based fracture probabilities in SA [20] found that Black Africans fell in the low-risk category and had slightly lower probability of fracture than Black Americans, this probability was less than the Indian and white population, and equivalent to the colored population.

1.4 Pathogenesis of Osteoporosis in Rheumatoid Arthritis

1.4.1 Pathogenesis

RA is characterized by synovial inflammation that occurs with synoviocyte activation and proliferation, whereby macrophages and other cells infiltrate. Systemic inflammation plays an essential role in the disruption of multiple homeostatic systems involved in bone health, including the Receptor Activator of Nuclear Factor β (RANK)/ RANK Ligand (RANKL)/Osteoprotegerin (OPG) and Wnt/β-catenin pathways [27].

T-lymphocytes express RANKL causing the production of pro-inflammatory stimuli including interleukin (IL)-1 and Tumor Necrosis Factor (TNF)α. These cytokines stimulate osteoclast maturation [4,6,27]. The mature osteoclasts express RANK on their surface after binding to RANKL, activating osteoclasts resulting in bone resorption [27].

Inflammation also influences Wnt proteins, which are a family of secreted proteins that regulates bone development and remodeling. Of considerable interest is that Wnt signaling through the canonical (ie Wnt/ β –catenin) pathway has been shown to increase bone mass through a number of mechanisms. These include stem cell renewal, stimulation of pre-osteoblast replication, osteoblastogenesis and osteoblast and osteocyte apoptosis inhibition. The Wnt/β-catenin pathway holds promise for new therapeutic targets either to add to or complement existing treatment [27].

1.4.2 Vitamin D and Parathyroid Hormone in RA

Another important system to be considered in bone health is the Vitamin or “Hormone” D/ PTH system. Of interest, a failure in Vitamin D metabolism has been described in patients with inflammatory rheumatic diseases. Vitamin D concentration correlates

positively with BMD. Patients with RA have altered Vitamin D/PTH system and this could participate in the pathogenesis of OP in rheumatic diseases, becoming another possible therapeutic target. It is now advised that Vitamin D deficiency should be targeted to suppress PTH [28].

1.4.3 RA related Risk Factors for Osteoporosis

1.4.3.1 Disease activity

Studies have been done to establish a relationship between disease activity and/or duration and the development of OP. Disease activity score (DAS) is an index of disease activity in RA, and it collates information from joints (swollen and tender), acute phase reactants and overall health into a single measure of rheumatoid inflammation. In doing this, it provides a disease activity measure in RA that is more valid than the individual components [29]. A recent Korean study, using the KORONA database, showed that disease activity factors as well as positivity for Rheumatoid Factor (RF) and ACCP, had no independent association with OP [13].

Yoshii [30] found that RA patients that received clinical remission within 6 months using the treat to target approach, had a similar BMD to the non-RA patients, and that patients achieving remission had significantly better BMD than patients not achieving remission. Hsu [31] conducted a prospective study in RA patients comparing the changes in BMD and disease markers over time, and the effect of antiosteoporosis treatment (AOT). Even with the use of AOT, the femoral BMD significantly decreased in patients with moderate and high disease activities but increased in the remission group. Patients that did not receive AOT in the moderate/ high group, showed greater decreases in BMD values at the hip (not the spine). Taiwanese Rheumatology experts [32] in their consensus recommendations endorsed the treat to target approach for RA

disease control, as cross-sectional studies suggest high disease activity as a risk factor for fracture especially vertebral.

1.4.3.2 Functional class

In 1978, the Health Assessment Questionnaire (HAQ) was developed and is the gold standard to assess functional status in patients with RA. The HAQ is a patient reported outcome measure consisting of eight categories of daily function [33]. The ACR, in 1991, developed its revised criteria to classify global functional status in RA, recognizing that health professionals may need to conduct a quick global assessment of functional class, and validation studies showed constancy between higher HAQ scores and higher global functional impairment [34]. The ACR does acknowledge the importance of self-reported questionnaires, preferably using the global functional status in combination with another instrument. The ACR functional class is graded from class 1 to class IV [34].

The Korean study [13] confirmed that advanced age, disease duration greater than 10 years and greater HAQ scores, were statistically significant independent factors for OP. Wafa [35], found in the Tunisian population that disease duration, high ESR, increased disability as evidenced by the HAQ score, corticosteroid use and post-menopause duration correlated with reduced BMD significantly(35). Kvien [36] had similar findings, and found that bone loss risk was almost doubled at the femoral neck in those patients with greater HAQ scores.

1.4.3.3 Autoantibodies

Evidence now indicates that RA antibodies specific to RA, especially ACCP, stimulates bone. The Pavia Early Arthritis Clinic investigated whether these antibodies affect

systemic BMD independent of other risk factors [37]. This study showed that ACCP causes bone loss early on and high titers of RF further increases this risk. Ileana [38], found that RF positivity was an independent risk factor for OP. Behrens [39], in his study of psoriatic arthritis found that ACCP seropositivity was associated with an almost 3-fold rise in erosive disease risk.

In a review article by Liorente [6], RA related antibodies are described as the drivers of bone resorption, by causing proliferation and maturation of osteoclasts, even before arthritis onset, resulting in bone loss either systemically or locally. Autoantibodies are also thought to release inflammatory cytokines from macrophages causing loss of bone mass through regulation of osteoclasts.

1.4.4 Glucocorticoids and Osteoporosis in RA

Glucocorticoids (GC) have been noted to have harmful effects on bone metabolism called GC induced OP (GIOP). GC can also cause sarcopenia and increase fall risk [5]. GC are used for its anti-inflammatory effects and reduces the activity of pro-inflammatory cytokines but causes resorption of bone by raising RANKL synthesis and decreasing OPG production. This greater bone resorption explains the response to anti- resorptive agents in managing of GIOP [5]. Almost all studies concur that there is a link between cumulative dose and loss of bone with subsequent fracture risk [13]. However, some studies have shown that low dose GC during flares may be beneficial in RA due to their anti-inflammatory effect, resulting in a neutral or even positive skeletal balance [5].

1.5 FRAX®

The OP risk factors in the world population have been well described. NOFSA, first published guidelines in 2000, which were updated and revised in 2010. The NOFSA guidelines states that 10 to 44% of women who have had a fragility fracture, have a T-score below -2.5 i.e., within the OP criteria range but most commonly fractures occur in individuals with osteopenia (T-score between -1.0 and -2.5) [7].

NOFSA recommends that a more accurate way to assess fracture risk is by collating the BMD measurement with clinical risk factors. These Clinical Risk Factors (CRF), identified by the WHO, are associated with a greater fracture risk than when BMD alone is considered [7].

The University of Sheffield launched the tool called FRAX® in 2008. It is a web-based assessment tool used to assess the ten-year probability of having a major osteoporotic fracture, using either certain risk factors alone or combining the risk factors with BMD results [40]. However, FRAX® has its limitations. Fracture probability differs in different regions in the world, where the incidence of fracture must be known. It also differs in different ethnic groups as incidence differs in these groups.

Until recently, SA did not have a FRAX based model as the studies related to incidence of fractures were sparse. However, in 2021, the hip fracture incidence rates were used to develop FRAX models in SA and is the first for sub-Saharan Africa. It also considers different incidence in different ethnic groups, with the Indian population having the highest incidence. The authors acknowledge the limitation that the fracture incidence was based on about 1/3 of the country's population, eight districts of 3 provinces and that they were unable to test the applicability to the whole country. Urbanization and other factors may also affect fracture rates [20].

The concern is that FRAX® incorporates RA as dichotomous predictor, and there is therefore concern about the performance of FRAX® in RA. However, most researchers are of the opinion that fracture risk may differ with more severe disease, longer disease or with treatment. This was not accounted for in the FRAX® system. FRAX® may underestimate fracture risk in patients with more severe RA, since it does not consider the underlying disease activity and resulting damage [41]. Specific to RA, several studies have shown that high disease activity (inflammation), disease duration > 10 years, higher overall doses of GC and greater Health Assessment Questionnaire (HAQ) scores, were significant independent risk factors for OP [13,38]. This is in addition to the classical risk factors such as higher age (>70), low BMI (<25), prior fragility fracture and osteoporotic hip fracture in a family member, lifestyle risks such as smoking, alcohol use more than 3 units per day, and evidence of inadequate calcium or vitamin D levels.

In a recent article, Miedany [42] commented on some of the limitations of FRAX, notably the dichotomous aspect of GC i.e. not accounting for cumulative dose or how long used for; previous fractures, where it is now established that the recency of a fracture is extremely important, as risks of second fractures are highest in the first 2 years after the index fracture; and fall propensity which is usually very high in RA patients with deforming disease.

1.6 Justification for the Current Study

There is limited data on OP in the RA population in South Africa, especially in the BSA population. OP remains silent until a fragility fracture occurs. Patients with RA are already at risk of other devastating co-morbidities, therefore it is imperative to establish

risk factors that could be used as predictors of OP and fracture risk in this population group.

2. AIM AND STUDY OBJECTIVES

2.1 Aim

The aim of the study is to evaluate OP in patients diagnosed with RA at the Chris Hani Baragwanath Academic Hospital (CHBAH)

2.2 Objectives

2.2.1 Primary Objective

To determine the risk factors for OP in Black South African (BSA) patients diagnosed with RA at CHBAH

3. METHODOLOGY

The study is a descriptive and comparative study of RA patients attending the Rheumatology outpatient clinic at CHBAH. A cohort of 120 BSA adults (>18years of age), fulfilling the 1987 American College of Rheumatology (ACR) criteria for RA and who have had DEXA scans, were selected. This comprised of 60 patients diagnosed with osteoporosis and 60 patients without osteoporosis, as defined by the NOFSA guidelines. The time frame for collection was from 2007 (the first availability of DEXA scans) to 2017.

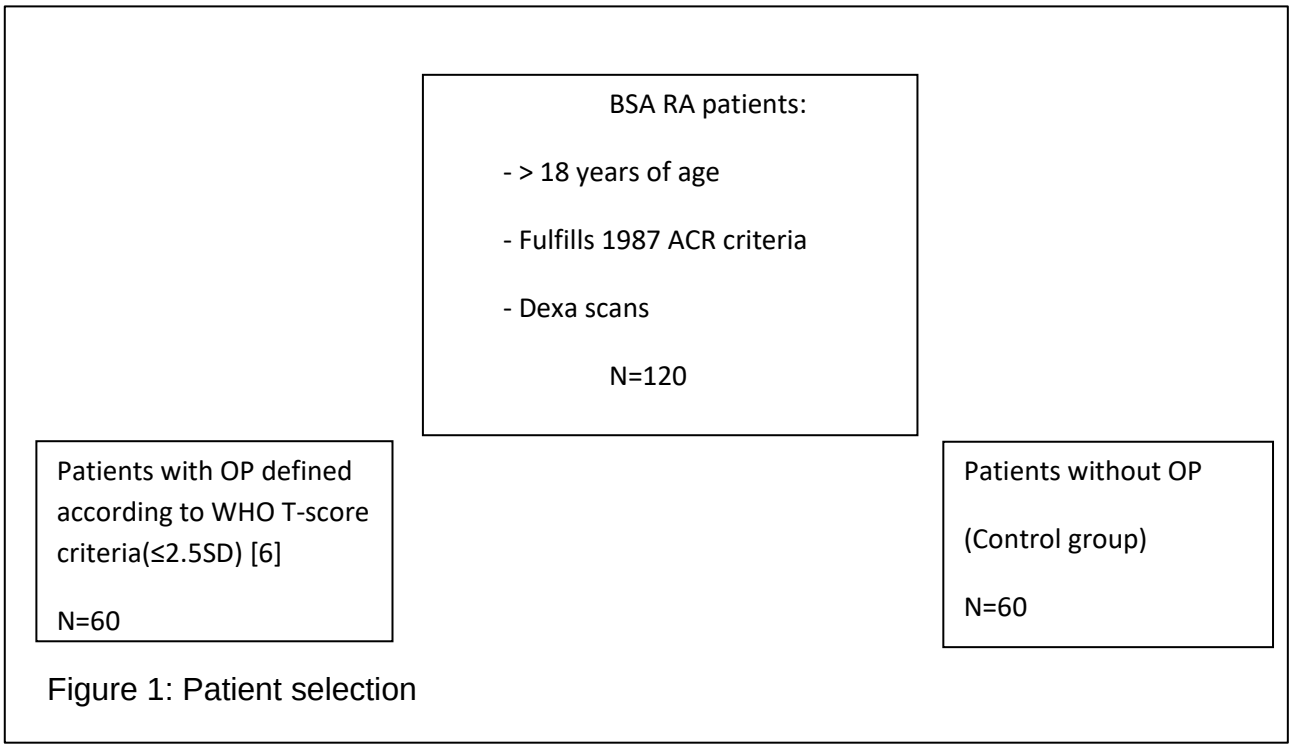


Figure 1: Patient selection

A Data Sheet (Appendix A) will be used to record the following variables:

A) Demographic Factors
   1. Age
   2. Gender
   3. Smoking and alcohol status
   4. HIV status
   5. Family history of fragility fractures, previous fragility fractures

B) Disease Factors
   1. ESR, DAS28ESR and ACR functional class
   2. Serology – RF, ACCP
   3. Treatments with Glucocorticoids (dose and duration), and DMARDS

C) DEXA characteristics
   1. T scores at the femoral neck, total hip and spine

4. DATA ANALYSIS

Data will be captured on a Microsoft Excel spreadsheet and will thereafter be transferred to SPSS [version 12] for analysis. Univariate comparisons of demographic factors, disease factors and T scores between patients with OP and without OP will be performed, using two-sided t tests for continuous variables and Chi squared tests for categorical variables. Possible predictors of OP will subsequently be entered into a multivariate logistic regression model with OP being the dependent variable. The level of significance for all analysis will be set at $p< 0.05$.

5. ETHICS

The Human Research Ethics Committee of the University of the Witwatersrand (Certificate no: M170705) granted ethical approval for this study.

6. TIMING

	February 2017	March 2017	April2017	May 2017	June 2017	July 2017	Aug 2017	Sept 2017	Oct 2017	Nov 2017	Dec 2017	Jan 2017
Literature Review												
Protocol Preparation												
Protocol Assessment												
Ethics Application												
Data Collection												
Data Analysis												
Writing up Paper												

7. FUNDING

The study will be self-funded for all expenses such as printing costs, laminating and binding. There will be no extra cost imposed on the hospital or the patients.

8. LIMITATIONS

The study is a retrospective study and accuracy will be dependent on written records, with data potentially being incomplete. It is a single centre study and results may not be generalizable.

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CHAPTER 2: SUBMISSIBLE ARTICLE

Osteoporosis in Black South Africans with Rheumatoid Arthritis

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Word count: 2117

Abstract Word Count: **229**

ABSTRACT

Background

Osteoporosis is a common comorbidity associated with rheumatoid arthritis (RA). The aim of this study was to determine the risk factors and possible predictors of osteoporosis in black patients with RA.

Methods

One hundred and twenty RA patients, 60 patients with and 60 without osteoporosis were studied. The demographics, disease activity, American college of Rheumatology (ACR) functional status, treatment and Dual Energy X-Ray Absorptiometry (DEXA) characteristics were then compared.

Results

The mean age of the overall cohort was 66.6 ± 9.5 years, majority (95.5%) were female, of which 97.4% were postmenopausal. The mean disease duration from diagnosis to the DEXA was 8.6 ± 6.2 years. Rheumatoid Factor (RF) positivity was 89.2% and Anti-cyclic Citrullinated Peptide (ACCP) positivity was 82.7%. The median (IQR) for Disease Activity Score 28 swollen and tender joint count using the erythrocyte sedimentation rate (DAS-28 ESR) was 3.4 (2.8-4.7) and the median (IQR) for ESR was 41(22,64.3) mm/hr ~~mmHg~~. There were significantly more patients treated with triple therapy in the no osteoporosis group 38 (63.3%) than the osteoporosis group 21 (35%) (p = 0.00). The ACR functional class was significantly worse in the RA patients with osteoporosis than the RA without osteoporosis [median (IQR), 2 (2, 3) vs 2 (1, 2), (p = 0.03, respectively.

Conclusion

This study found that worse ACR functional class was significantly associated with osteoporosis. In addition, the use of triple therapy had a protective effect. Early recognition of the risk factors for osteoporosis should be sought, with prompt preventative measures, screening and treatment.

Introduction

Rheumatoid arthritis (RA) is a common inflammatory arthritis affecting up to 1 % of adults worldwide [1]. It is a destructive joint disease resulting in substantial pain, significant disability, and impairment of quality of life if untreated. Osteoporosis is a well-recognized comorbidity of RA and is more frequent than in the general population [2].

In RA, women have a twofold increase in osteoporosis while men show a twofold increase of reduced bone mass compared to patients without RA [3]. The Italian Study Group found a frequency of osteoporosis in patients with RA of 28,8% at the lumbar spine and 36,2% at the femoral neck [4]. More recently, the Korean Observational Study Network for Arthritis (KORONA) database reported the frequency of osteoporosis in patients with RA to be as high as 46,8% [2]. while in India the prevalence of osteoporosis in RA is 22% [5]. The Total Management of Risk Factors in RA patients to Lower Morbidity and Mortality (TOMORROW) study, found the prevalence of vertebral fractures to be as high as 45,5% in patients with RA [6].

Osteoporosis is more common in inflammatory conditions, suggesting a correlation between osteoclasts which are the cells that cause bone loss or resorption, and cytokines that are pro-inflammatory [7]. It is now well recognized that the inflammatory state in early RA results in cytokine release causing osteoclast activation and differentiation through the classic RANK/RANKL/OPG pathway and the Wnt/DKK/sclerostin pathway, all leading to loss of bone [8]. Even before disease onset, RA specific antibodies particularly rheumatoid factor (RF) and anti-citrullinated cyclic peptide (ACCP) antibody, are pathogenic mechanisms for development of osteoporosis [8]. Glucocorticoids are extensively used in RA, often used as a bridging

therapy due to their efficacy in reducing inflammation but also have proven harmful effects on bone health. The incidence of fracture in RA patients with early disease exposed to glucocorticoids as compared to non-exposed RA patients, is doubled [9]. The development of osteoporosis in RA leads to a decline in the quality of life and substantial increase in the costs of rehabilitation and treatment. Osteoporotic fractures yield an enormous economic burden, from the direct burden of hospitalizations and physician visits, which in 2002 ranged from 12,2 to 179 billion dollars per year, as well as indirect costs, related to decreased productivity due to morbidity and premature mortality [10]. Mortality rate from fractures as a result of osteoporosis is higher than mortality from other causes such as cervical cancer, uterine cancer or breast cancer [11].

Bone loss in RA is associated with both traditional and RA specific risk factors, the interplay of both resulting in a heightened risk of developing osteoporosis. High disease activity, disease duration > 10 years, higher doses of glucocorticoids, higher fall risk and poor functionality as measured by the Health Assessment Questionnaire (HAQ), are significant independent risk factors for osteoporosis in RA [2, 12]. In addition, there may be traditional risk factors such as older age (>70), low BMI (<25), prior fragility fracture and family history of osteoporotic hip fracture, lifestyle factors such as smoking, alcohol use more than 3 units per day, and inadequate calcium or vitamin D levels.

The aim of the study was to determine the risk factors for osteoporosis in black South African (BSA) patients diagnosed with RA attending a tertiary care facility in South Africa.

PATIENTS AND METHODOLOGY

A retrospective study of 120 BSA patients attending an arthritis clinic in Johannesburg, South Africa was performed. All patients were black adults (≥18 years of age at disease diagnosis), fulfilling the 1987 American College of Rheumatology (ACR) criteria for RA [13] and who had DEXA scans done.

Of the 120 RA patients studied, 60 had osteoporosis and 60 had no osteoporosis.

Data collected were patient demographics, traditional osteoporosis risk factors such as smoking and significant alcohol use defined as ≥3 units per day, history of fractures, symptom duration prior to DEXA, RA disease activity, autoantibodies, ACR functional status and disease modifying antirheumatic (DMARD) therapy. Autoantibodies included rheumatoid factor (RF) and anti-cyclic citrullinated peptide (ACCP). Disease activity was determined at the visit prior to the DEXA using DAS28 ESR [14]. The physical function was evaluated using the 1991 ACR functional class (FC) [15]. Disease activity markers ESR, CRP and the ACR FC was taken in the visit closest to the DEXA scan but not more than a year before. Osteoporosis was defined as a T-score ≤2.5 SD at any of the 3 sites (total hip, femoral neck or spine) measured using the WHO criteria [16]. The DMARD escalation strategy starts with monotherapy methotrexate (MTX), then to combination therapy with MTX, sulphasalazine and chloroquine (CHQ) (triple therapy) if not in remission or low disease activity defined by DAS28 ESR. Leflunomide is used if combination therapy fails.

Statistical analysis was performed using SPSS. Bivariate comparisons of demographic factors, disease factors and T-scores between patients with osteoporosis and without osteoporosis was performed, using two-sided t tests for

continuous variables and Chi$squared$ tests for categorical variables. Possible predictors of osteoporosis were subsequently entered into a multivariate logistic regression model with osteoporosis being the dependent variable. The level of significance for all analysis was set at $p< 0.05$.

RESULTS

The median (IQR) age of the overall cohort was 67 years with the majority being postmenopausal females. The disease duration from diagnosis to having the DEXA was 8 years. A minority consumed alcohol 7 (6.1%) or were ever smokers 11(9.6%). A previous osteoporotic fracture was recorded in only 8 (7%) patients. Most of the patients were seropositive; RF positivity was 89.2% and ACCP positivity was 82.7% and had moderate disease activity with a DAS-28 ESR, median (IQR) of 3.4 (2.8,4.7) prior to the DEXA scan (Table 1). There was a total of 8 previous fractures in the entire cohort, however it is not known if these were fragility fractures.

Most patients (83.3%) were treated with corticosteroids for an average of two years. The majority were treated with methotrexate, approximately half were on triple therapy and a third on leflunomide. There were significantly more patients treated with triple therapy in the no osteoporosis group (63.3%) than the osteoporosis group (35%) ($p = 0.00$).

The ACR FC was significantly worse in the RA with osteoporosis than the RA without osteoporosis group [median (IQR), 2 (2, 3) vs 2 (1, 2), ($p = 0.03$), respectively.

Table 1. Demographics, clinical features, and drug therapy in 120 rheumatoid arthritis patients, with and without osteoporosis

Variable	***All patients (n=120)***	***RA with OP (n-60)***	***RA no OP (n=60)***	***OR (95% CI)***	***P value***
Female gender, n (%)	114 (95.0)	59 (98.3)	55 (91.7)	5.4 (0.6, 47.4)	0.20
Age in years, median (IQR))	67.0 (61.0, 72.8)	68.0 (63.0, 73.8)	66.0 (57.2, 71.0)	-	0.088
Disease duration from diagnosis to DEXA in years, median (IQR)	8 (4, 13)	8 (4, 14)	8 (4.2, 12)	-	0.62
Postmenopausal, n (%)	111 (97.4)	57 (96.6)	54 (98.2)	0.53 (0.05, 5.99)	1.00
Alcohol history (>3units per day), n (%)	7 (6.1)	5 (8.6)	2 (3.5)	2.59 (0.48, 13.96)	0.44
Smoking history, n (%)	11 (9.6)	6 (10.3)	5 (8.8)	1.2 (0.34, 4.18)	1.00
RF positive, n (%)	107 (89.2)	56 (93.3)	51 (85.0)	2.47 (0.72, 8.52)	0.24
Anti-ACPA, n (%)	81 (82.7)	46 (82.1)	35 (83.3)	0.92 (0.32, 2.66)	1.00
DAS28-ESR, median (IQR)*	3.4 (2.8, 4.7)	3.3 (2.8, 4.8)	3.7 (2.7, 4.7)	-	0.95
ESR mm/hr, median (IQR)*	41 (22, 64.3)	41.5 (22.5, 70.8)	41 (21.3, 60.8)	-	0.67
ACR functional class, median (IQR)	**2 (1, 2)**	**2 (2, 3)**	**2 (1, 2)**	**-**	**0.03**
Previous history of fractures	8 (7.0)	5 (8.6)	3 (5.3)	1.7 (0.39, 7.46)	0.72
HIV positive, n (%)	4 (3.4)	3 (5.0)	1 (1.7)	3.05 (0.31, 30.22)	0.62
Drug therapy					
Prednisone, n (%)	100 (83.3)	50 (83.3)	50 (83.3)	1 (0.38, 2.61)	1.00
>7.5mg, n (%)	24 (24.0)	9 (18.0)	15 (30.0)	0.51 (0.2, 1.31)	0.24
duration in months, median (IQR)	25.5 (12, 57)	28 (10, 61.3)	25 (16, 51.5)	-	0.68
Methotrexate, n (%)	112 (93.3)	56 (93.3)	56 (93.3)	1 (0.24, 4.2)	1.00
Chloroquine, n (%)	83 (69.2)	37 (61.7)	46 (76.7)	0.49 (0.22, 1.08)	0.11
Sulphasalazine, n (%)	75 (62.5)	32 (53.3)	43 (71.7)	0.45 (0.21, 0.96)	0.06
Triple Rx	**59 (49.2)**	**21 (35)**	**38 (63.3)**	**0.31 (0.15, 0.66)**	**0.00**
Leflunomide, n (%)	43 (35.8)	20 (33.3)	23 (38.3)	0.8 (0.38, 1.7)	0.70

OP = osteoporosis, SD = standard deviation, IQR = interquartile range

Table 2. DEXA characteristics of 120 rheumatoid patients, with and without osteoporosis

Variable	***All patients (n=120)***	***RA with OP (n-60)***	***RA no OP (n=60)***	***OR (95% CI)***	***P value***
Femoral neck					
T score, median (IQR)	-1.7 (-2.33, -0.68)	-2.30(-2.80, -1.80)	-0.80 (-1.58, 0.45)	-	<0.0001
osteopenia, n (%)	54 (45.8)	29 (50.0)	25 (41.7)	1.4 (0.68, 2.9)	0.46
osteoporosis, n (%)	26 (22)	26 (44.8)	0 (0.0)	-	0.000
Total hip					
T score, median (IQR)	-1.5 (2.30, -0.30)	-2.25 (-2.83, -1.60)	-0.5 (-1.28, 0.40)	-	<0.0001
osteopenia, n (%)	46 (39)	27 (46.6)	19 (31.7)	1.88 (0.89, 3.98)	0.131
osteoporosis, n (%)	25 (21.2)	25 (43.1)	0 (0.0)		0.000
Spine					
T score, median (IQR)	-2.1 (-3.00, -0.90)	-3.00 (-3.60, -2.60)	-1.10 (-1.70, 0.10)	-	<0.0001
osteopenia, n (%)	40 (33.6)	9 (15.0)	31 (52.5)	0.16 (0.07, 0.38)	<0.0001
osteoporosis, n (%)	47 (39.5)	47 (78.3)	0 (0.0)	-	0.000

In the osteoporosis group, T-scores were worse at the spine than the femoral neck and total hip. Osteopenia was frequently recorded in the non-osteoporosis group.

Multivariate Logistic regression showed that combination therapy with MTX, CHQ and sulphasalazine therapy was significantly protective of osteoporosis OR=3.9 (1.1-8.6), p= 0.001. Poorer functional class was also a significant predictor of osteoporosis (OR = 1.9 (1.1-3.6), p= 0.022. (Table 3).

Table 3: Predictors of osteoporosis

	OR (95% CI)	**P value**
Triple therapy	3.87(1.75,8.55)	0.001
ACR Functional Class	1.99(1.10,3.58)	0.022

Higher spine T-scores were observed in patients on triple therapy as was seen in patients with better functionality (ACR functional class I, II). The median (IQR) spine T score for patients on triple therapy was statistically higher -1.70 (-2.70, -0.80), compared to those not on triple therapy -2.55 (-3.38, -0.90), p value = 0.023. The median (IQR) femoral neck T scores for patients with ACR FC I/II was statistically higher -1.60 (-2.30, -0.80), compared to patients with ACR FC III/IV -2.10 (-2.93, -1.40), p value = 0.041.

Discussion

Similar to other studies, osteoporosis and osteopenia was common in this cohort of black South Africans with RA. We identified poor functionality as a predictor of osteoporosis and triple DMARD therapy as protective. To the best of our knowledge, there are very few studies describing risk factors for osteoporosis in patients with RA in South Africa.

Many studies have demonstrated that RA patients have a substantially increased fracture risk than patients with no RA [11]. Chen et. al. [17] conducted a meta-analysis showing the relative risk (pooled) of fracture at the vertebrae in RA patients was 2.34 (95% CI 2.05 – 2.63, $P < 0.0001$).

Like other studies [2,18] our study showed ESR and DAS 28 ESR not to be independent risk factors for osteoporosis. This is in contrast to other studies [19,20] that showed that higher ESR was statistically associated with the occurrence of osteoporosis.

Similar to this study, poor functionality in RA has been associated with osteoporosis in other studies [2,20,4]. Worse modified health assessment questionnaire (mHAQ) scores were found to be an independent risk factor for osteoporosis [21] with bone loss almost doubling in the lumbar spine and in the femoral neck in patients with high HAQ scores. Despite using a different measure of physical function, the ACR functional classification, we found poorer functionality to be associated with osteoporosis.

Glucocorticosteriods (GC) are an important cause of osteoporosis in RA with 10% of patients on long-term treatment developing fractures and radiographic evidence of vertebral fractures being found in 30-40% of patients [22]. Despite the average duration of steroid use being over 2 years, we found no association with osteoporosis in our study. The study was limited as we were unable to calculate cumulative dose.

The use of triple therapy i.e., MTX, Sulphasalazine and CHQ, was significantly protective against the development of osteoporosis. This may be explained by better disease activity control although this was not reflected by the ESR or the DAS-28-ESR. We postulate that this may be because disease activity measures were taken at one point in time rather than an average value over time.

There are several limitations to the study. The retrospective cross-sectional nature of this study is a major shortcoming with respect to missing data and inconsistences in documenting clinical problems in case records. Moreover, improvement in early detection of osteoporosis due to greater availability of DEXA over time might have underestimated these comorbidities previously. Also, we were unable to quantify the cumulative prednisone dose.

Conclusion

Osteoporosis and therefore fragility fractures are more frequent in RA. This study found that worse ACR functional class was significantly associated with osteoporosis. In addition, the use of triple therapy had a protective effect. Early recognition of the risk factors for osteoporosis should be sought, with prompt preventative measures, screening, and treatment.

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DATA COLLECTION SHEET **PARTICIPANT NUMBER _____**

PART A **DEMOGRAPHIC AND CLINICAL FEATURES**

1. AGE RANGE	18 -20	21 - 30	31 - 40	41 - 50	51 - 60	> 60
Exact						

2. GENDER	Male	Female

3. HIV STATUS	Postive	Negative	Unknown

4. FRACTURES			
A. FAMILY Hx of HIP FRACTURES	Yes	No	Unknown
B. PREVIOUS FRAGILITY FRACTURES	Yes	No	Unknown

5. SMOKING	Current	Ex	None	Unknown

6. ALCOHOL INTAKE	Yes	No	Ex	Unknown

7. DISEASE DURATION		
Range	<10 Years	>= 10 Years
Exact		

8. GLUCOCORTICOID USE	Yes	No

IF YES	
Baseline Dose of GC (mg/day)	
Duration of GC Use (Months)	
Highest GC dose used (mg/day)	

9. ACTIVITY MARKERS			
RF Positivity	Yes	No	Titre if Yes
ACCP Positivity	Yes	No	Titre if Yes
Baseline ESR (mm/hr)			
Baseline CRP (mg/dl)			

10. ACTIVITY SCORES			
CDAI	Yes	No	If YES, Value
HAQ Score	Yes	No	If YES, Value

11. DMARDS	Yes	No	Name :

PART B **DEXA SCAN AND OSTEOPOROSIS TREATMENT**

1. DATE OF DEXA SCAN	

2. ONSET OF RA TO DEXA SCAN (YEARS)	<5 YEARS	>= 5 YEARS
Exact		

3. DEXA RESULT (1st)			
SITE	T SCORE	*CLASSIFICATION	Z SCORE
SPINE			
FEMORAL NECK (L or R, whichever is lowest)			
TOTAL HIP (L or R, whichever is lowest)			

4. VERTEBRAL DEFORMITY ASSESSMENT (1st)		
Fractures	YES	NO
If Yes, Number of Fractures		

5. TREATMENT	Yes	No
If YES, NAME OF DRUG		

6. REPEAT DEXA SCAN	YES	NO
If YES, Date		

7. DEXA RESULT (2nd)			
SITE	T SCORE	*CLASSIFICATION	Z SCORE
SPINE			
FEMORAL NECK (L or R, whichever is lowest)			
TOTAL HIP (L or R, whichever is lowest)			

8. VERTEBRAL DEFORMITY ASSESSMENT (2nd)		
Fractures	YES	NO
If Yes, Number of Fractures		

*Classification
N = Normal
OPN = Osteopenia
OP = Osteoporosis

Appendix B

R14/49 Dr Tania Naidoo

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170705

NAME: (Principal Investigator)	Dr Tania Naidoo
DEPARTMENT:	Internal Medicine Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Osteoporosis in Patients with Rhematoid Arthritis at Chris Hani Baragwanath Academic Hospital
DATE CONSIDERED:	28/07/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Ling Winchow

UNIVERSITY OF THE WITWATERSRAND
OFFICE OF THE DEPUTY VICE CHANCELLOR RESEARCH
03 OCT 2017
RESEARCH OFFICE HREC (Medical) RECEIVED
JOHANNESBURG

APPROVED BY: Prof P Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 31/07/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting `the study was initially reviewed. In this case, the study was initially reviewed in July and will therefore be due in the month of July each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES